What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient (Updated October 14, 2011)

Panel's Recommendations:

- ***The Panel recommends the following as preferred regimens for antiretroviral (ARV)-naive patients:***
  - ***efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) (AI)***
  - ***ritonavir-boosted atazanavir + tenofovir/emtricitabine (ATV/r + TDF/FTC) (AI)***
  - ***ritonavir-boosted darunavir + tenofovir/emtricitabine (DRV/r + TDF/FTC) (AI)***
  - ***raltegravir + tenofovir/emtricitabine (RAL + TDF/FTC) (AI)***
- ***A list of Panel-recommended alternative and acceptable regimens can be found in Table 5a and Table 5b.***
- ***Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions.***
- ***Based on individual patient characteristics and needs, in some instances, an alternative regimen may actually be a preferred regimen for a patient.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

More than 20 approved ARV drugs in 6 mechanistic classes are available to design combination regimens. These 6 classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), CCR5 antagonists, and integrase strand transfer inhibitors (INSTIs).

The Panel provides recommendations for preferred, alternative, and acceptable regimens; regimens that may be acceptable but more definitive data are needed; and regimens that may be acceptable but should be used with caution (**Tables 5a and 5b**). Potential advantages and disadvantages of the components recommended as initial therapy for ARV-naive patients are listed in **Table 6** to guide prescribers in choosing the regimen best suited for an individual patient. **Table 7** provides a list of agents or components not recommended for initial treatment.

CONSIDERATIONS WHEN SELECTING A FIRST ANTIRETROVIRAL REGIMEN FOR ANTIRETROVIRAL THERAPY-NAIVE PATIENTS

Data Used for Making Recommendations

The Panel's recommendations are primarily based on clinical trial data published in peer-reviewed journals and data prepared by manufacturers for Food and Drug Administration (FDA) review. In selected cases, the Panel considers data presented in abstract format in major scientific meetings. The first criterion for selection of evidence on which to base recommendations is published information from a randomized, prospective clinical trial with an adequate sample size that demonstrates durable viral suppression and immunologic enhancement (as evidenced by increase in CD4 count). Few of these trials include clinical endpoints, such as development of AIDS-defining illness or death. Thus, assessment of regimen efficacy and potency is primarily based on surrogate marker endpoints (HIV RNA and CD4 responses). The Panel reviewed data from randomized clinical trials to arrive at preferred, alternative, or acceptable ratings noted in **Tables 5a and 5b**. "Preferred regimens" are those regimens studied in randomized controlled trials and shown to have optimal and durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. "Alternative regimens" are those regimens that are effective but have potential disadvantages when compared with preferred regimens. In certain situations and based on individual patient characteristics and needs, a regimen listed as an alternative may actually be the preferred regimen for a specific patient. Some regimens are classified as "Acceptable regimens" because of reduced virologic activity, lack of efficacy data from large clinical trials, or other factors (such as greater toxicities, the need for additional testing, pill burden, or drug interaction potential) compared with preferred or alternative regimens.

Lastly, the Panel classified some regimens as "regimens that are acceptable but should be used with caution" because of certain safety or efficacy concerns explained in **Table 5b**.

Factors to Consider When Selecting an Initial Regimen

Regimen selection should be individualized on the basis of a number of factors, including the following:

- comorbid conditions (e.g., cardiovascular disease, chemical dependency, liver disease, psychiatric disease, renal diseases, or tuberculosis);
- potential adverse drug effects;
- potential drug interactions with other medications;
- pregnancy or pregnancy potential;
- result of genotypic drug-resistance testing;
- gender and pretreatment CD4 count if considering nevirapine (NVP);
- HLA-B*5701 testing if considering abacavir (ABC);
- coreceptor tropism assay if considering maraviroc (MVC);
- patient adherence potential; and
- convenience (e.g., pill burden, dosing frequency, and food and fluid considerations).

Considerations for Therapies

Appendix B, Tables 1–6 provide a listing of characteristics, such as formulations, dosing recommendations, pharmacokinetics, and common adverse effects, of individual ARV agents. Additionally, **Appendix B, Table 7** provides clinicians with ARV dosing recommendations for patients who have renal or hepatic insufficiency.

An initial ARV regimen generally consists of two NRTIs in combination with an NNRTI, a PI (preferably boosted with ritonavir [RTV]), an INSTI (namely RAL), or a CCR5 antagonist (namely MVC). In clinical trials, NNRTI-, PI-, INSTI-, or CCR5 antagonist-based regimens have all resulted in HIV RNA decreases and CD4 cell increases in a large majority of patients *[1-7]*.

Tables 5a and 5b include the Panel's recommendations for initial therapy.

Table 5a. Preferred and Alternative Antiretroviral Regimens for Antiretroviral Therapy-Naive Patients (Updated October 14, 2011)

A combination ART regimen generally consists of two NRTIs + one active drug from one of the following classes: NNRTI, PI (generally boosted with RTV), INSTI, or a CCR5 antagonist. Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and the patient's comorbid conditions. Refer to Table 6 for a list of advantages and disadvantages and Appendix B, Tables 1–6 for dosing information for individual ARV agents listed below. The regimens in each category are listed in alphabetical order.

Preferred Regimens (Regimens with optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use) **The preferred regimens for nonpregnant patients are arranged by chronological order of FDA approval of components other than nucleosides and, thus, by duration of clinical experience.**	
NNRTI-Based Regimen • EFV/TDF/FTC[1] **(AI)** **PI-Based Regimens** *(in alphabetical order)* • ATV/r + TDF/FTC[1] **(AI)** • DRV/r (once daily) + TDF/FTC[1] **(AI)** **INSTI-Based Regimen** • RAL + TDF/FTC[1] **(AI)** **Preferred Regimen for Pregnant Women[2]** • LPV/r (twice daily) + ZDV/3TC[1] **(AI)**	**Comments** **EFV** should not be used during the first trimester of pregnancy or in women of childbearing potential trying to conceive or not using effective and consistent contraception. **TDF** should be used with caution in patients with renal insufficiency. **ATV/r** should not be used in patients who require >20 mg omeprazole equivalent per day. Refer to Table 15a for dosing recommendations regarding interactions between ATV/r and acid-lowering agents.
Alternative Regimens (Regimens that are effective and tolerable but have potential disadvantages compared with preferred regimens. An alternative regimen may be the preferred regimen for some patients.)	
NNRTI-Based Regimens *(in alphabetical order)* • EFV + ABC/3TC[1] **(BI)** • RPV/TDF/FTC[1] **(BI)** • RPV + ABC/3TC[1] **(BIII)** **PI-Based Regimens** *(in alphabetical order)* • ATV/r + ABC/3TC[1] **(BI)** • DRV/r + ABC/3TC[1] **(BIII)** • FPV/r (once or twice daily) + ABC/3TC[1] or TDF/FTC[1] **(BI)** • LPV/r (once or twice daily) + ABC/3TC[1] or TDF/FTC[1] **(BI)** **INSTI-Based Regimen** • RAL + ABC/3TC[1] **(BIII)**	**Comments** • Use **RPV** with caution in patients with pretreatment HIV RNA >100,000 copies/mL. • Use of proton pump inhibitors is contraindicated with **RPV**. • **ABC** should not be used in patients who test positive for HLA-B*5701. • Use **ABC** with caution in patients with known high risk of cardiovascular disease or with pretreatment HIV RNA >100,000 copies/mL. (See text.) **Once-daily LPV/r** is not recommended in pregnant women.

[1]3TC may substitute for FTC or vice versa.
[2]For more detailed recommendations on ARV use in an HIV-infected pregnant woman, refer to the *Perinatal Guidelines* available at http://aidsinfo.nih.gov/guidelines.

The following combinations in the recommended list above are available as coformulated fixed-dose combination: ABC/3TC, EFV/TDF/FTC, LPV/r, RPV/TDF/FTC, TDF/FTC, and ZDV/3TC.

Acronyms: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ARV = antiretroviral, ATV/r = atazanavir/ritonavir, DRV/r = darunavir/ritonavir, EFV = efavirenz, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, INSTI = integrase strand transfer inhibitor, LPV/r = lopinavir/ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, PI = protease inhibitor, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, TDF = tenofovir, ZDV = zidovudine

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Table 5b. Acceptable Antiretroviral Regimens for Treatment-Naive Patients
(Updated October 14, 2011)

Acceptable Regimens (CI) (Regimens that may be selected for some patients but are less satisfactory than preferred or alternative regimens) **and Regimens that may be acceptable but more definitive data are needed (CIII)**

NNRTI-Based Regimen
- EFV + ZDV/3TC[1] **(CI)**
- NVP + (TDF/FTC[1] or ZDV/3TC[1]) **(CI)**
- NVP + ABC/3TC[1] **(CIII)**
- RPV + ZDV/3TC[1] **(CIII)**

PI-Based Regimens
- ATV + (ABC or ZDV)/3TC[1] **(CI)**
- ATV/r + ZDV/3TC[1] **(CI)**
- DRV/r + ZDV/3TC[1] **(CIII)**
- FPV/r + ZDV/3TC[1] **(CI)**
- LPV/r + ZDV/3TC[1] **(CI)**

INSTI-Based Regimen
- RAL + ZDV/3TC[1] **(CIII)**

CCR5 Antagonist-Based Regimens
- MVC + ZDV/3TC[1] **(CI)**
- MVC + TDF/FTC[1] or ABC/3TC[1] **(CIII)**

Comments

NVP
- NVP should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C).[2]
- NVP should not be used in women with pre-ART CD4 count >250 cells/mm^3 or in men with pre-ART CD4 count >400 cells/mm^3.

Use **NVP** and **ABC** together with caution because both can cause HSRs within the first few weeks after initiation of therapy.

ZDV can cause bone marrow suppression, lipoatrophy, and rarely lactic acidosis with hepatic steatosis.

LPV/r (twice daily) + ZDV/3TC is the preferred regimen for pregnant women.

ATV/r is generally preferred over unboosted ATV. Unboosted ATV may be used when RTV boosting is not possible.

MVC
Perform tropism testing before initiation of therapy with MVC. MVC may be considered in patients who have only CCR5-tropic virus.

Regimens that may be acceptable but should be used with caution (Regimens that have demonstrated virologic efficacy in some studies but have safety, resistance, or efficacy concerns. See comments below.)

PI-Based Regimens
- SQV/r + TDF/FTC[1] **(CI)**
- SQV/r + (ABC or ZDV)/3TC[1] **(CIII)**

Comments
- **SQV/r** was associated with PR and QT prolongation in a healthy volunteer study.
- Baseline ECG is recommended before initiation of **SQV/r**.
- **SQV/r** is not recommended in patients with any of the following:
  1. pretreatment QT interval >450 msec
  2. refractory hypokalemia or hypomagnesemia
  3. concomitant therapy with other drugs that prolong QT interval
  4. complete AV block without implanted pacemaker
  5. risk of complete AV block

[1]3TC maybe substituted with FTC or vice versa.
[2]Refer to **Appendix B, Table 7** for the criteria for Child-Pugh classification.

Acronyms: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ATV = atazanavir, ATV/r = atazanavir/ritonavir, AV = atrioventricular, DRV/r = darunavir/ritonavir, ECG = electrocardiogram, EFV = efavirenz, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, HSR = hypersensitivity reaction, INSTI = integrase strand transfer inhibitor, LPV/r = lopinavir/ritonavir, msec = millisecond, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, SQV/r = saquinavir/ritonavir, TDF = tenofovir, ZDV = zidovudine

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
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NNRTI- versus PI- versus INSTI- versus CCR5 Antagonist-Based Regimens

EFV has been compared with a number of other drugs (other NNRTIs, PIs, RAL, MVC), in combination regimens containing two NRTIs *[3-9]*. To date, no regimen has proven superior to EFV-based regimens with respect to virologic responses.

NNRTI- versus PI-Based Regimens
RTV-boosted PI-based regimens have shown good virologic and immunologic responses but are often associated with more gastrointestinal symptoms, whereas EFV-based regimens are associated with more rash and central nervous system adverse effects. Both types of regimens may be associated with hepatic transaminase elevations *[10]*.

Drug resistance to most PIs requires multiple mutations in the HIV protease gene, and it seldom develops after early virologic failure *[11]*, especially when RTV boosting is used. At least partial resistance to EFV, NVP, or rilpivirine (RPV), however, is conferred by a single mutation in the reverse transcriptase gene, and it may develop rapidly after virologic failure. An estimated 8% of newly infected patients in the United States carry NNRTI-resistant viruses *[12]*. Because of the concern for primary resistance in the antiretroviral therapy (ART)-naive population, genotypic testing results should be used to guide the selection of the initial ARV regimen. (See **Drug-Resistance Testing**.) In terms of convenience, coformulation of EFV/TDF/FTC or RPV/TDF/FTC allows for once-daily dosing with a single tablet. Most PI-based regimens include RTV, may be dosed once or twice daily, and require more pills in the regimen. Drug-drug interactions are important with both kinds of regimens, but more clinically significant interactions are seen with RTV-boosted PI regimens.

Other Treatment Options
Another option for initial therapy is the combination of TDF/FTC and RAL *[6]*. This combination showed similar virologic efficacy compared with TDF/FTC/EFV up to 156 weeks *[13]* and is generally well tolerated. No clinical trial data exist comparing INSTI-based with PI-based regimens. RAL requires twice-daily dosing, has a low genetic barrier for selection of resistance mutations, and has had relatively limited use with other dual-NRTI combinations. MVC has been approved for use in ART-naive patients, based on data from the MERIT study comparing MVC/zidovudine (ZDV)/lamivudine (3TC) with EFV + ZDV/3TC *[7]*.

The discussions below focus on the rationale for the Panel's recommendations, based on the efficacy, safety, and other characteristics of different agents within the individual drug classes.

NNRTI-BASED REGIMENS (1 NNRTI + 2 NRTIs)

Summary: NNRTI-Based Regimens

Five NNRTIs (delavirdine [DLV], EFV, etravirine [ETR], NVP, and RPV) are currently FDA approved.

NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs involve the prevalence of NNRTI-resistant viral strains in ART-naive patients *[12, 14-16]* and the low genetic barrier of NNRTIs for development of resistance. Resistance testing should be performed to guide therapy selection for ART-naive patients (see **Drug-Resistance Testing**). All NNRTIs except for ETR require only a single mutation to confer resistance, and cross resistance affecting these NNRTIs is common. ETR, an NNRTI approved for ART-experienced patients, has *in vitro* activity against some viruses with mutations that confer resistance to DLV, EFV, and NVP *[17]*. However, in RPV-treated patients, the presence of RPV-resistant mutations at virologic failure is common and may confer cross resistance to ETR *[18]*.

On the basis of clinical trial results and safety data, the Panel recommends that EFV, RPV, or NVP may be used as part of an initial regimen. In most instances, EFV is preferred, based on its potency and tolerability (as discussed below). EFV should not be used in pregnant women (especially during the first trimester) or in women of childbearing potential who are planning to conceive or who are sexually active with men and not using effective and consistent contraception.

RPV may be used as an alternative NNRTI option in treatment-naive patients **(B)**, whereas NVP may be used as an acceptable NNRTI option **(C)** in women with pretreatment CD4 counts ≤250 cells/mm^3 or in men with pretreatment CD4 counts ≤400 cells/mm^3. (See discussions below.)

Among the NNRTIs, DLV is dosed three times daily, has the least supportive clinical trial data, and appears to have the least antiviral activity. As such, DLV is **not recommended** as part of an initial regimen **(BIII)**. ETR at a dose of 200 mg twice daily is approved for use in treatment-experienced patients with virologic failure *[19]*. In a small, randomized, double-blind, placebo-controlled trial, ETR 400 mg once daily was compared with EFV 600 mg once daily (both in combination with two NRTIs) in treatment-naive subjects. Seventy-nine and 78 participants were randomized to the ETR and EFV arms, respectively. At 48 weeks, 76% of the ETR recipients and 74% of the EFV recipients achieved plasma HIV RNA <50 copies/mL. Neuropsychiatric side effects were more frequently reported in the EFV recipients than in the ETR recipients *[20]*. These results suggest that once-daily ETR may be a potential NNRTI option in treatment-naive patients. However, more data are required and, pending results from larger trials, the panel cannot recommend ETR as initial therapy at this time.

Following is a more detailed discussion of NNRTI-based regimens for initial therapy.

EFV as Preferred NNRTI

Large randomized, controlled trials and cohort studies of ART-naive patients have demonstrated potent viral suppression in EFV-treated patients; a substantial proportion of these patients had HIV RNA <50 copies/mL during up to 7 years of follow-up *[1-2, 21]*. Studies that compared EFV-based regimens with other regimens demonstrated that the combination of EFV with two NRTIs was superior virologically to some PI-based regimens, including indinavir (IDV) *[3]*, ritonavir-boosted lopinavir (LPV/r) *[4]*, and nelfinavir (NFV) *[8]* and to triple-NRTI–based regimens of ABC, ZDV, and 3TC or ABC, TDF, and 3TC *[22-23]*. EFV-based regimens also had comparable virologic activity when compared with NVP- *[24-25]*, atazanavir (ATV)- *[5]*, RAL- *[6],* or MVC-based *[7]* regimens.

The ACTG 5142 study randomized patients to receive two NRTIs together with either EFV or LPV/r (or an NRTI-sparing regimen of EFV and LPV/r) *[4]*. The dual-NRTI and EFV regimen was associated with a better virologic response than the dual-NRTI and LPV/r regimen at 96 weeks, whereas the dual-NRTI with LPV/r regimen was associated with a better CD4 response and less drug resistance after virologic failure.

The 2NN trial compared EFV with NVP, both given with stavudine (d4T) and 3TC, in ART-naive patients. Virologic responses were similar for both drugs, although NVP was associated with greater toxicity and did not meet criteria for noninferiority compared with EFV *[24]*. Two randomized controlled trials compared EFV + two NRTIs with RPV + two NRTIs. Most patients received TDF/FTC as the NRTI pair. Pooled data evaluated at 48 weeks demonstrated comparable virologic efficacy for the two study groups, except in participants in each group who had baseline HIV RNA >100,000 copies/mL. Among participants who had baseline viremia at this level, a greater proportion of subjects randomized to RPV experienced virologic failure *[18]*.

Limitations of EFV are its central nervous system adverse effects, which usually resolve over a few weeks, and its potential teratogenic effects. In animal reproductive studies, EFV at drug exposure levels similar to those achieved in humans caused major congenital anomalies in the central nervous system of nonhuman primates *[26]*. In humans, several cases of neural tube defects in newborns of mothers exposed to EFV during the first trimester of pregnancy have been reported *[27-28]*. Therefore, EFV is not recommended in pregnant women during the first trimester of pregnancy or in women with high pregnancy potential (women of childbearing potential who are trying to conceive or who are sexually active with men and are not using effective and consistent contraception) **(AIII)**.

Studies that use EFV and dual-NRTI combinations (ABC, didanosine [ddI], d4T, TDF, or ZDV together with FTC or 3TC) show durable virologic activity, although there may be differences among the various combinations chosen. (See **Dual-NRTI Options**.) A single tablet coformulated with TDF, FTC, and EFV provides one-tablet, once-daily dosing and is currently the preferred NNRTI-based regimen **(AI)**.

RPV as Alternative NNRTI

In two large, multinational, randomized, double-blind clinical trials, RPV (25 mg once daily) was compared with EFV (600 mg once daily), each in combination with two NRTIs. In a pooled analysis of the two studies, 83% of RPV-treated subjects and 80% of EFV-treated subjects had plasma HIV RNA <50 copies/mL at 48 weeks *[18, 29-30]*. Although overall RPV demonstrated noninferiority to EFV, for participants with higher pretreatment HIV RNA (>100,000 copies/mL), virologic failure occurred more frequently in those randomized to receive RPV. Subjects with virologic failure on RPV were also more likely to have genotypic resistance to other NNRTIs (EFV, ETR, and NVP) and to have resistance to their prescribed NRTIs.

Drug discontinuations because of adverse effects were more common with EFV than RPV. The frequency of depressive disorders and discontinuations due to depressive disorders were similar between the two arms, whereas dizziness, abnormal dreams, rash, and hyperlipidemia were more frequent with EFV.

At higher than the approved dose of 25 mg, RPV (75 mg once daily or 300 mg once daily) may prolong the QTc interval. As a result, RPV should be used cautiously when coadministered with a drug having a known risk of torsades de pointes. Although RPV has shown no teratogenicity in animal studies, data on pharmacokinetics and safety of RPV in pregnant HIV-infected women are insufficient at this time. RPV should not be given to adolescents younger than 18 years of age because appropriate dosing information in this age group is lacking.

A fixed-dose combination tablet of RPV/TDF/FTC allows for one-tablet once-daily dosing. RPV must be administered with a meal. Its oral bioavailability may be significantly reduced in the presence of acid-lowering agents. RPV should be used with caution with antacids and H_2-receptor antagonists. RPV use with proton pump inhibitors is contraindicated. **Table 15b** provides guidance on the timing of RPV administration when it is used together with antacids or H_2 receptor antagonists.

Based on limited data on durability of treatment responses (48 weeks) and the lower virologic response compared with EFV in patients with high pretreatment viral loads, the panel recommends RPV/TDF/FTC as an alternative regimen for initial therapy **(BI)**. Caution should be exercised when using RPV in patients with plasma HIV RNA >100,000 copies/mL, given the higher RPV virologic failure rates and the greater probability of ETR resistance at the time of failure observed in this population during clinical trials.

NVP as Acceptable NNRTI

In the 2NN trial, 70% of participants in the EFV arm and 65.4% in the twice-daily NVP arm had virologic suppression (defined as HIV RNA <50 copies/mL) at 48 weeks. This difference did not reach criteria necessary to demonstrate noninferiority of NVP *[24]*. Two deaths were attributed to NVP use. One resulted from fulminant hepatitis and one from staphylococcal sepsis as a complication of Stevens-Johnson syndrome.

In the ARTEN trial, ART-naive participants were randomized to NVP 200 mg twice daily or NVP 400 mg once daily or RTV-boosted ATV (ATV/r), all in combination with TDF/FTC. The proportion of participants in each arm who achieved the primary endpoint of having at least two consecutive plasma HIV RNA levels <50 copies/mL before Week 48 was similar (66.8% for NVP vs. 65.3% for ATV/r). However, more participants in the NVP arms than the ATV/r arm discontinued study drugs before Week 48 because of adverse events (13.6% vs. 2.6%) or lack of efficacy (8.4% vs. 1.6%). NNRTI- and/or NRTI-resistance mutations were selected in 29 of 44 (65.9%) participants who experienced virologic failure while on NVP, whereas resistance mutations were not detected in any of the 28 participants who had virologic failure on ATV/r *[31]*.

Serious hepatic events have been observed when NVP was initiated in ART-naive patients. These events generally occur within the first few weeks of treatment. In addition to experiencing elevated serum transaminases, approximately half of the patients also develop skin rash, with or without fever or flu-like symptoms. Retrospective analysis of reported events suggests that women with higher CD4 counts appear to be at highest risk *[32-33]*. A 12-fold higher incidence of symptomatic hepatic events was seen in women (including pregnant women) with CD4 counts >250 cells/mm^3 at the time of NVP initiation compared with women with CD4 counts $\leq$250 cells/mm^3 (11.0% vs. 0.9%). An

increased risk was also seen in men with pretreatment CD4 counts >400 cells/mm^3 compared with men with pretreatment CD4 counts ≤400 cells/mm^3 (6.3% vs. 1.2%). Most of these patients had no identifiable underlying hepatic abnormalities. In some cases, hepatic injuries continued to progress despite discontinuation of NVP *[33-34]*. In contrast, other studies have not shown an association between baseline CD4 counts and severe NVP hepatotoxicity *[35-36]*. Symptomatic hepatic events have not been reported with single-dose NVP given to mothers or infants for prevention of perinatal HIV infection.

On the basis of the safety and efficacy data discussed above, the Panel recommends that NVP be considered as an acceptable NNRTI **(C)** as initial therapy for women with pretreatment CD4 counts ≤250 cells/mm^3 or in men with pretreatment CD4 counts ≤400 cells/mm^3. Patients who experience CD4 count increases to levels above these thresholds as a result of NVP-containing therapy can safely continue therapy without an increased risk of adverse hepatic events *[37]*.

At the initiation of NVP, a 14-day lead-in period at a dosage of 200 mg once daily should be instituted before increasing to the maintenance dosage of 400 mg per day (as an extended-release 400-mg tablet once daily or 200-mg immediate-release tablet twice daily). Some experts recommend monitoring serum transaminases at baseline, at 2 weeks, then 2 weeks after dose escalation, and then monthly for the first 18 weeks. Clinical and laboratory parameters should be assessed at each visit.

PI-BASED REGIMENS (RTV-BOOSTED OR UNBOOSTED PI + TWO NRTIs)

Summary: PI-Based Regimens

PI-based regimens (particularly with RTV-boosting) have demonstrated virologic potency and durability in treatment-naive subjects. Unlike NNRTI- and INSTI-based regimens, resistance mutations are seldom detected at virologic failure. In patients who experience virologic failure while on their first PI-based regimen, few or no PI mutations are detected at failure *[31, 38]*. Each PI has its own virologic potency, adverse effect profile, and pharmacokinetic properties. The characteristics, advantages, and disadvantages of each PI are listed in **Table 6** and **Appendix B, Table 3**. In selecting a boosted PI-based regimen for an ART-naive patient, clinicians should consider factors such as dosing frequency, food requirements, pill burden, daily RTV dose, drug interaction potential, baseline lipid profile, toxicity profile of the individual PI, and pregnancy status. (See the ***Perinatal Guidelines*** for specific recommendations in pregnancy *[39]*.)

A number of metabolic abnormalities, including dyslipidemia and insulin resistance, have been associated with PI use. The currently available PIs differ in their propensity to cause these metabolic complications, which are also dependent on the dose of RTV used as a pharmacokinetic boosting agent. Two large observational cohort studies suggested that LPV/r, IDV, fosamprenavir (FPV), or ritonavir-boosted fosamprenavir (FPV/r) may be associated with increased rates of myocardial infarction (MI) or stroke *[40-41]*. Both studies had too few patients receiving ATV/r or DRV/r to be included in the analysis. Ritonavir-boosted saquinavir (SQV/r) can prolong the PR and QT intervals on electrocardiogram (ECG). The degree of QT prolongation is greater than that seen with some other boosted PIs. Therefore, SQV/r should be used with caution in patients at risk of or who use concomitant drugs that may potentiate these ECG abnormalities *[42]*.

The potent inhibitory effect of RTV on the cytochrome P (CYP) 450 3A4 isoenzyme allows the addition of low-dose RTV to other PIs as a pharmacokinetic booster to increase drug exposure and prolong the plasma half-life of the active PI. This allows for reduced dosing frequency and/or pill burden, which may improve overall adherence to the regimen. The increased trough concentration (C_{min}) may improve the ARV activity of the primary PI, which can be beneficial when the patient harbors HIV strains with reduced susceptibility to the PI *[43-45]* and also may contribute to the lower risk of resistance upon virologic failure compared with unboosted PIs. The drawbacks associated with this strategy are the potential for increased risk of hyperlipidemia and a greater potential of drug-drug interactions from the addition of RTV. In patients without pre-existing PI resistance, support for the use of once-daily boosted PI regimens that use only 100 mg per day of RTV is growing. This is because these regimens tend to cause fewer gastrointestinal side effects and less metabolic toxicity than regimens that use RTV at a dose of 200 mg per day.

The Panel uses the following criteria to distinguish between preferred versus alternative PIs in ART-naive patients: (1) demonstrated superior or noninferior virologic efficacy when compared with at least one other PI-based regimen, with at least published 48-week data; (2) RTV-boosted PI with no more than 100 mg of RTV per day; (3) once-daily dosing; (4) low pill count; and (5) good tolerability. Using these criteria, the Panel recommends ATV/r (once daily) and DRV/r (once daily) as preferred PIs.

Preferred PI (in alphabetical order, by active PI component)

RTV-Boosted ATV (ATV/r). RTV boosting of ATV, given as two pills once daily, enhances the concentrations of ATV and improves virologic activity compared with unboosted ATV in a clinical trial *[46]*.

The CASTLE study compared once-daily ATV/r with twice-daily LPV/r, each in combination with TDF/FTC, in 883 ARV-naive participants. In this open-label, noninferiority study, analysis at 48 weeks *[47]* and at 96 weeks *[48]* showed similar virologic and CD4 responses of the two regimens. More hyperbilirubinemia and less gastrointestinal toxicity were seen in the ATV/r arm. This study supports the designation of ATV/r + TDF/FTC as a preferred PI-based regimen **(AI)**.

The main adverse effect associated with ATV/r is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Nephrolithiasis has also been reported in patients who received RTV-boosted or unboosted ATV *[49]*. ATV/r requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that raise gastric pH, such as antacids, H_2 antagonists, and particularly proton pump inhibitors, may impair absorption of ATV. **Table 15a** provides recommendations for use of ATV/r with these agents.

RTV-Boosted DRV (DRV/r). The ARTEMIS study compared DRV/r (800/100 mg once daily) with LPV/r (once or twice daily), both in combination with TDF/FTC, in a randomized, open-label, noninferiority trial. The study enrolled 689 ART-naive participants. At 48 weeks, DRV/r was noninferior to LPV/r. The virologic response rates were lower in the LPV/r arm among those participants whose baseline HIV RNA levels were >100,000 copies/mL. Grades 2 to 4 adverse events, primarily diarrhea, were seen more frequently in LPV/r recipients *[50]*. At virologic failure, no major PI mutations were detected in participants randomized to either arm *[38]*. At 96 weeks, virologic response to DRV/r was superior to response to LPV/r *[51]*. Based on these data, the Panel recommends DRV/r + TDF/FTC as a preferred PI-based regimen **(AI).** No randomized controlled trial exists to evaluate the efficacy of DRV/r with other two-NRTI combinations. A small retrospective study suggested that DRV/r plus ABC/3TC may be effective in treatment-naive patients for up to 48 weeks *[52]*. Based on this preliminary information, the Panel recommends this combination as an alternative PI-based regimen **(BIII).**

Alternative PI (in alphabetical order, by active PI component)

RTV-Boosted FPV (FPV/r) (once or twice daily). FPV/r is recommended as an alternative PI. The KLEAN trial compared twice-daily FPV/r with LPV/r, each in combination with ABC and 3TC, in ART-naive patients. At Weeks 48 and 144, similar percentages of subjects achieved viral loads of <400 copies/mL *[53-54]*. The frequency and severity of adverse events did not differ between the regimens. Twice-daily FPV/r was noninferior to twice-daily LPV/r. Based on the preference for once-daily regimens with no more than 100 mg/day of RTV, twice-daily FPV is now considered an alternative choice.

In a study comparing once-daily FPV/r (1,400 mg with RTV 200 mg once daily) with NFV *[55]*, similar virologic efficacy was reported in both arms. A comparative trial of once-daily FPV/r (1,400/100 mg) with once-daily ATV/r, both in combination with TDF/FTC, was conducted in 106 ARV-naive participants *[56]*. Similar virologic and CD4 benefits were seen with both regimens. The small sample size of this study precludes the assessment of superior or noninferior virologic efficacy required for a preferred PI. Collectively, FPV/r regimens, with once- or twice-daily dosing, are recommended as alternative PI-based regimens.

RTV-Boosted LPV (LPV/r) (coformulated). LPV/r is the only available coformulated boosted PI. It can be given once or twice daily. However, the need for 200 mg/day of RTV, and the higher rate of gastrointestinal side effects and

hyperlipidemia when compared with boosted PIs using RTV 100 mg/day, make it an alternative rather than preferred PI for ART-naive patients. Early studies showed that LPV/r was superior to NFV in maintaining suppressed viral loads *[57]*. A 7-year follow-up study of LPV/r and two NRTIs showed sustained virologic suppression in patients who were maintained on the originally assigned regimen *[58]*. Results of clinical trials that compared LPV/r with ATV/r, DRV/r, FPV/r, or SQV/r are discussed in the respective sections of this document. The ACTG 5142 study showed that the regimen of twice-daily LPV/r plus two NRTIs had decreased virologic efficacy when compared with EFV plus two NRTIs. However, the CD4 response was greater with LPV/r, and there was less drug resistance associated with virologic failure *[4]*.

Several trials have evaluated different formulations and dosages of LPV/r administered once or twice daily *[50, 59-60]*. In the largest trial that compared once-daily with twice-daily LPV/r, both in combination with TDF/FTC, 664 ART-naive participants were randomized to receive once- or twice-daily soft-gel capsules or once- or twice-daily tablets for 8 weeks; at Week 8, all participants received the tablet formulation and maintained their same randomized dosing schedule *[61]*. At Week 48, 77% of once-daily and 76% of twice-daily LPV/r recipients achieved viral loads <50 copies/mL. Rates of moderate to severe drug-related diarrhea were similar between the two groups. In addition to diarrhea, major adverse effects of LPV/r include insulin resistance and hyperlipidemia, especially hypertriglyceridemia; these required pharmacologic management in some patients. In the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) and French observational cohorts, cumulative use of LPV/r was associated with a slightly increased risk of MI *[40-41]*. Once-daily LPV/r should not be used in patients who have HIV mutations associated with PI resistance because higher LPV trough levels may be required to suppress resistant virus. LPV/r given twice daily is the preferred PI for use in pregnant women **(A)** *[39]*. Once-daily dosing should not be used in this situation, especially during the third trimester, when LPV levels are expected to decline. For more detailed information regarding ART drug choices and related issues in pregnancy, see the ***Perinatal Guidelines*** *[39]*.

Acceptable PI-Based Component

ATV. Unboosted ATV is given once daily and has fewer adverse effects on lipid profiles than other available PIs. Three studies compared ATV-based combination regimens with either NFV- or EFV-based regimens. These studies established similar virologic efficacy among ATV 400 mg once daily and both comparator treatment groups in ARV-naive patients after 48 weeks of therapy *[5, 46, 62-63]*.

Unboosted ATV may be an acceptable initial therapy for patients when a once-daily regimen without RTV is desired and for patients with underlying risk factors indicating that hyperlipidemia may be particularly undesirable **(C)**. ATV should be used with RTV-boosting if TDF or EFV are used concomitantly because these two agents can lower the concentrations of ATV. ATV requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that raise gastric pH, such as antacids, H_2 antagonists, and proton pump inhibitors, may significantly impair ATV absorption. Proton pump inhibitors should not be used in patients who are taking unboosted ATV. H_2 antagonists and antacids should be used with caution and with careful dose separation. (See **Tables 14 and 15a**.)

PI Component that May be Acceptable but Should be Used with Caution

RTV-Boosted SQV (SQV/r). The GEMINI study compared SQV/r (1,000/100 mg twice daily) with LPV/r, both given twice daily, in combination with TDF/FTC given once daily, in 337 ART-naive participants who were monitored over 48 weeks. Similar levels of viral suppression and increases in CD4 counts were seen in both arms *[64]*. Triglyceride levels were higher in the LPV/r arm. The SQV/r regimen has a higher pill burden and requires twice-daily dosing and 200 mg of RTV. In a healthy volunteer study, SQV/r use at the recommended dose was associated with increases in both QT and PR intervals. The degree of QT prolongation was greater than that seen with some other boosted PIs used at their recommended doses. Rare cases of torsades de pointes and complete heart block have been reported in post-marketing surveillance. Based on these findings, an ECG is recommended before initiation of SQV/r. SQV/r is not recommended for patients with any of the following conditions: documented congenital or acquired QT prolongation, pretreatment QT interval of >450 milliseconds (msec), refractory hypokalemia or hypomagnesemia, complete atrioventricular (AV) block without implanted pacemakers, at risk of complete AV block, or receiving other drugs that prolong QT interval *[42]*. Based on these restrictions and because there are several other preferred or alternative PI options, the Panel recommends that SQV/r may be acceptable but should be used with caution in selected ARV-naive patients **(C)**.

INSTI-BASED REGIMENS (INSTI + TWO NRTIs)

RAL. RAL is an INSTI approved for use in ART-naive patients based on results of STARTMRK, a Phase III study that compared RAL (400 mg twice daily) with EFV (600 mg once daily), each in combination with TDF/FTC, in ART-naive subjects. This multinational double-blind, placebo-controlled study enrolled 563 subjects with plasma HIV-1 RNA levels >5,000 copies/mL. At Week 48, similar numbers of subjects achieved HIV-1 RNA levels <50 copies/mL in both groups (86.1% and 81.9% for RAL and EFV, respectively, p <0.001 for noninferiority). CD4 counts rose by 189 cells/mm3 in the RAL group versus 163 cells/mm3 in the EFV group. Serious adverse events occurred at a similar frequency in both groups *[6]*. At 156 weeks, virologic and immunologic responses remained similar in both groups with no new safety concerns identified *[13]*. Based on these data, the Panel recommends RAL + TDF/FTC (or 3TC) as a preferred regimen for ART-naive patients **(AI)**. In a small single-arm pilot study of 35 subjects who received a regimen of RAL + ABC/3TC, 91% of participants had HIV RNA <50 copies/mL at Week 48 *[65]*. Based on these preliminary data, RAL + ABC/3TC may be used as an alternative INSTI-based regimen **(BIII)**.

Comparisons of RAL-based regimens with other regimens in ART-naive subjects have not yet been reported, and experience with RAL is less than with EFV or boosted PIs for initial therapy. In addition, RAL must be administered twice daily, a potential disadvantage when compared with some other regimens. RAL, like EFV, has a lower genetic barrier to resistance than RTV-boosted PIs, and resistance mutations were observed at approximately the same frequency in the comparative trial.

CCR5 ANTAGONIST-BASED REGIMENS (CCR5-Antagonist + Two NRTIs)

The MERIT study compared the CCR5 antagonist MVC with EFV, both in combination with ZDV/3TC, in a randomized, double-blind trial in ART-naive participants *[7]*. Only participants who had CCR5-tropic virus and had no evidence of resistance to any drugs used in the study were enrolled (n = 721). At 48 weeks, virologic suppression (defined as HIV RNA <400 copies/mL) was seen in 70.6% of MVC recipients and in 73.1% of EFV recipients, and HIV RNA <50 copies/mL was observed in 65.3% of MVC recipients and in 69.3% of EFV recipients. The HIV RNA <50 copies/mL results did not meet the criteria set by the investigators to demonstrate noninferiority for MVC in this study. CD4 count increased by an average of 170 cells/mm3 in the MVC arm and by 144 cells/mm3 in the EFV arm. Through 48 weeks, compared with EFV, more participants discontinued MVC because of lack of efficacy (11.9% vs. 4.2%), whereas fewer participants discontinued MVC because of toxicity (4.2% vs. 13.6%). Follow-up results at 96 weeks demonstrated durable responses *[66]*. In a post-hoc reanalysis using a more sensitive viral tropism assay, 15% of patients with non-R5 screening virus were excluded from analysis, and their retrospective exclusion resulted in similar response rates in both arms, using either the HIV RNA criteria of <400 or <50 copies/mL. Based on the results, FDA approved MVC for use in regimens for ART-naive patients. Because MVC requires twice-daily dosing, requires an expensive tropism assay prior to use, and experience with regimens other than ZDV/3TC is limited, the Panel recommends MVC + ZDV/3TC as an acceptable regimen for use in ART-naive patients **(CI)**. Although the MERIT trial used ZDV/3TC as its NRTI backbone, pending further data, many clinicians would favor the combination of MVC with TDF/FTC or ABC/3TC **(CIII)**.

DUAL-NRTI OPTIONS AS PART OF INITIAL COMBINATION THERAPY

Summary: Dual-NRTI Components

Dual NRTIs are commonly used in combination with an NNRTI, a PI (usually boosted with RTV), an INSTI, or a CCR5 antagonist. Most dual-NRTI combinations used in clinical practice consist of a primary NRTI plus 3TC or FTC. Both 3TC and FTC have few adverse effects but may select for the M184V resistance mutation, which confers high-level resistance to both drugs; a modest decrease in susceptibility to ddI and ABC; and improved susceptibility to ZDV, d4T, and TDF *[67]*.

All NRTIs except ddI can be taken with or without food. Adherence may be additionally improved with once-daily dosing (available for all NRTIs except d4T and ZDV) and with fixed-dosage combinations, such as ABC/3TC, TDF/FTC (with or without EFV or RPV), or ZDV/3TC.

The Panel's recommendations on specific dual-NRTI options are made on the basis of virologic potency and durability, short- and long-term toxicities, the propensity to select for resistance mutations, and dosing convenience.

Preferred Dual-NRTI

TDF/FTC (coformulated). TDF is a nucleotide analog with potent activity against both HIV and hepatitis B virus (HBV) and with a long intracellular half-life that allows for once-daily dosing. The fixed-dose combinations of TDF/FTC and TDF/FTC/EFV are both administered as one tablet once daily and are designed to improve adherence.

TDF, when used with either 3TC or FTC as part of an EFV-based regimen in ART-naive patients, demonstrated potent virologic suppression *[21]* and was superior to ZDV/3TC in virologic efficacy up to 144 weeks *[68]*. In the 934 study, more participants in the ZDV/3TC arm developed loss of limb fat (as assessed by dual-energy x-ray absorptiometry [DXA]) and anemia at 96 and 144 weeks compared with the TDF/FTC arm *[68]*. Emergence of the M184V mutation was less frequent than with ZDV/3TC, and no participant had developed the K65R mutation after 144 weeks of therapy, in contrast to other studies in which TDF was combined with 3TC. TDF with FTC or 3TC in combination with several boosted PIs and RAL has been studied in randomized clinical trials; all such trials demonstrate good virologic benefit *[6, 47, 50, 56, 60]*.

TDF/FTC was compared with ABC/3TC in the ACTG 5202 study *[69]* and the HEAT trial *[70]*. Inferior virologic responses were observed in participants randomized to ABC/3TC who had a pretreatment HIV RNA >100,000 copies/mL. This was not confirmed by the results from the HEAT trial. (See the ABC/3TC section below for more detailed discussion.)

Renal impairment, manifested by increases in serum creatinine, glycosuria, hypophosphatemia, and acute tubular necrosis, has been reported with TDF use *[71-72]*. Risk factors may include advanced HIV disease, greater treatment experience, and pre-existing renal impairment *[73]*. Renal function, urinalysis, and electrolytes should be monitored in patients who are on TDF. In patients who have some degree of pre-existing renal insufficiency (creatinine clearance [CrCl] <50 mL/min), TDF dosage adjustment is required. (See **Appendix B, Table 7** for dosage recommendations.) However, because available dosage adjustment guidelines for renal dysfunction are based on pharmacokinetic studies only and not on safety and efficacy data, the use of alternative NRTIs (especially ABC) may be preferred over dose-adjusted TDF in this setting.

Concomitant use of some PIs can increase TDF concentrations, and studies have suggested a greater risk of renal dysfunction when TDF is used in PI-based regimens *[71, 74-77]*. TDF has been used in combination with PIs without renal toxicity in several clinical trials that involved patients who had CrCl >50–60 mL/min. Furthermore, in two randomized studies comparing TDF/FTC to ABC/3TC, participants receiving TDF/FTC experienced a significantly greater decline in bone mineral density *[78-79]*.

TDF plus either FTC or 3TC is the preferred NRTI combination, especially for patients coinfected with both HIV and HBV because these drugs have activity against both viruses. The use of a single HBV-active NRTI (e.g., 3TC or FTC) can lead to HBV resistance and is not recommended. (See **Hepatitis B (HBV)/HIV Coinfection**.)

Alternative Dual NRTI

ABC/3TC (coformulated) for Patients who Test Negative for HLA-B*5701.
In a comparative trial of ABC/3TC and ZDV/3TC (both given twice daily and combined with EFV), participants from both arms achieved similar virologic responses. The ABC-treated participants experienced a greater CD4 T-cell increase at 48 weeks *[80]*. The ACTG 5202 study, a randomized controlled trial in more than 1,800 participants, evaluated the efficacy and safety of ABC/3TC versus TDF/FTC when used in combination with either EFV or RTV-boosted ATV. Treatment randomization was stratified based on a screening HIV RNA of <100,000 copies/mL or ≥100,000 copies/mL. HLA-B*5701 testing was not required prior to study entry, which may have influenced the

results of the trial with respect to some of the safety and tolerability endpoints. A Data Safety Monitoring Board recommended early termination of the ≥100,000 copies/mL stratification group because of a significantly shorter time to study-defined virologic failure in the ABC/3TC arm compared with the TDF/FTC arm *[69]*. This difference in virologic failure between arms was observed regardless of whether the third active drug was EFV or ATV/r. There was no difference between ABC/3TC and TDF/FTC in time to virologic failure for participants who had plasma HIV RNA < 100,000 copies/mL at screening. TDF/FTC has a more favorable safety and tolerability profile than ABC/3TC *[81]*.

In another study (HEAT), 688 participants received ABC/3TC or TDF/FTC in combination with once-daily LPV/r. A subgroup analysis according to baseline HIV RNA of <100,000 copies/mL or ≥100,000 copies/mL yielded similar percentages of participants with HIV RNA <50 copies/mL at 96 weeks for the two regimens (63% vs. 58% for those who had <100,000 copies/mL and 56% vs. 58% for those who had ≥100,000 copies/mL, respectively) *[70]*. The ASSERT study compared open label ABC/3TC with TDF/FTC in 385 HLA-B*5701-negative, ART-naive patients; all study subjects also received EFV. At 48 weeks, a lower proportion of the ABC/3TC-treated subjects had HIV RNA <50 copies/mL (59%) compared with those receiving TDF/FTC (71%, difference 11.6%, 95% confidence interval [CI] 2.2 to 21.1) *[82]*.

ABC has the potential for serious hypersensitivity reactions (HSRs). Clinically suspected HSRs have been observed in 5%–8% of patients who start ABC. The risk of this reaction is highly associated with the presence of the HLA-B*5701 allele *[83-84]*. (See **HLA-B*5701 Screening**.) HLA-B*5701 testing should precede the use of ABC. ABC should not be given to patients who test positive for HLA-B*5701, and based on test results, ABC hypersensitivity should be noted on the patient's allergy list. Patients who test HLA-B*5701 negative are less likely to experience an HSR, but they should be counseled about the symptoms of the reaction.

An association between ABC use and MI was first reported in the D:A:D study. This large, multinational observational study group found that recent (within 6 months) or current use of ABC, but not TDF, was associated with an increased risk of MI, particularly in participants with pre-existing cardiac risk factors *[40, 85]*. Since this D:A:D study, multiple studies have explored this association. Some studies have found an association *[86-89]*; others have found a weak or no association *[41, 90-93]*. Multiple studies have also been conducted to evaluate potential mechanistic pathways, including endothelial dysfunction, increased platelet reactivity, leukocyte adhesion, inflammation, and hypercoagulability *[94-101]* that may underlie the association between ABC use and an increased risk of MI. However, to date, no consensus has been reached either on the association of ABC use with MI risk or a possible mechanism for the association.

The fixed-dose combination of ABC/3TC allows for once-daily dosing. Pending additional data, ABC/3TC should be used with caution in individuals who have plasma HIV RNA levels ≥100,000 copies/mL and in persons at higher risk of cardiovascular disease. However, the combination of ABC/3TC remains a good alternative dual-NRTI option for some ART-naive patients **(BI)**.

Acceptable Dual NRTI

ZDV/3TC (coformulated). The dual-NRTI combination of ZDV/3TC has extensive durability, safety, and tolerability experience *[3, 5, 8, 22, 102-104]*. A fixed-dose combination of ZDV/3TC is available for one-tablet, twice-daily dosing. Selection of the 3TC-associated M184V mutation has been associated with increased susceptibility to ZDV. In a comparative trial of ABC/3TC versus ZDV/3TC (both given twice daily and combined with EFV), even though virologic responses were similar in both arms, the CD4 count increase was greater in the ABC/3TC-treated patients than in the ZDV/3TC-treated patients *[80]*.

Bone marrow suppression, manifested by macrocytic anemia and/or neutropenia, is seen in some patients. ZDV also is associated with gastrointestinal toxicity, fatigue, and possibly mitochondrial toxicity, including lactic acidosis/hepatic steatosis and lipoatrophy. Because of its greater toxicity compared with TDF/FTC or ABC/3TC and the need for twice-daily dosing, the Panel recommends ZDV/3TC as an acceptable, rather than a preferred or alternative, dual-NRTI option **(CI)**.

ZDV/3TC remains a preferred option in pregnant women. This dual NRTI has the most pharmacokinetic, safety, and efficacy data for both mother and newborn. For more detailed information regarding ARV drug choices and related issues in pregnancy, see the ***Perinatal Guidelines*** *[39]*.

NRTIs and Hepatitis B Virus (HBV). Three of the currently approved NRTIs—FTC, 3TC, and TDF—have activity against HBV. Most HBV/HIV-coinfected patients should use coformulated TDF/FTC (or TDF + 3TC) as their NRTI backbone to provide additional activity against HBV and to avoid selection of HBV mutation that confers resistance to 3TC/FTC. Importantly, patients who have HBV/HIV coinfection may be at risk of acute exacerbation of hepatitis after initiation or upon discontinuation of TDF, 3TC, or FTC *[105-107]*. Thus, these patients should be monitored closely for clinical or chemical hepatitis if these drugs are initiated or discontinued. (See **Hepatitis B (HBV)/HIV Coinfection** and **Initiating Antiretroviral Therapy**.)

ALL-NRTI REGIMENS

Triple-NRTI regimens studied in several clinical trials have shown suboptimal virologic activity *[22-23, 108-111]*.

ABC/3TC/ZDV (coformulated). ABC/3TC/ZDV is the only triple-NRTI combination for which randomized, controlled trials are available. ABC/3TC/ZDV demonstrated comparable ARV activity to IDV-based *[103-104]* and NFV-based regimens *[111]* but was inferior virologically to an EFV-based regimen *[22]*. This combination is **generally not recommended (BI)** and should be used only when a preferred, an alternative, or an acceptable NNRTI-, PI-, or INSTI- based regimen is less desirable because of concerns about toxicities, drug interactions, or regimen complexity.

ZDV/3TC + TDF. The DART study demonstrated that the combination of ZDV/3TC + TDF has antiviral activity *[112]*. However, because comparative data with standard regimens are not available, this combination **cannot be recommended** in routine clinical practice **(BIII)**.

ZDV/3TC + ABC + TDF. A quadruple-NRTI regimen of ZDV/3TC + ABC + TDF first showed comparable virologic responses to an EFV-based regimen in a small pilot study *[113]*. A larger study randomized 322 subjects to receive TDF/FTC combined with EFV, ATV/RTV, or a quadruple-NRTI regimen with ZDV and ABC. Although the threshold of noninferiority for the protocol-defined virologic response was satisfied by the quadruple-NRTI regimen, the proportion of patients reaching HIV RNA $\leq$50 copies/mL was lower with the quadruple-NRTI regimen and the rate of serious toxicity was twice as high as that observed with the EFV-based regimen *[114]*. Thus, this regimen **cannot be recommended (BI)**.

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Updated October 14, 2011)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
NNRTIs (in alphabetical order)		**NNRTI Class Advantages:** • Long half-lives	**NNRTI Class Disadvantages:** • Greater risk of resistance at the time of failure with NNRTIs than with PIs • Potential for cross resistance • Skin rash • Potential for CYP450 drug interactions (See Tables 14, 15b, and 16b.) • Transmitted resistance to NNRTIs more common than resistance to PIs
	EFV	• Virologic responses equivalent or superior to all comparators to date • Once-daily dosing • Coformulated with TDF/FTC	• Neuropsychiatric side effects • Teratogenic in nonhuman primates. Several cases of neural tube defect reported in infants of women exposed to EFV in the first trimester of pregnancy. EFV use should be avoided in women with potential for pregnancy and is contraindicated in the first trimester. • Dyslipidemia
	NVP	• No food effect • Fewer lipid effects than EFV • Once-daily dosing with extended-release tablet formulation	• Higher incidence of rash, including rare but serious HSRs (Stevens-Johnson syndrome or toxic epidermal necrolysis), than with other NNRTIs • Higher incidence of hepatotoxicity, including serious and even fatal cases of hepatic necrosis, than with other NNRTIs • Contraindicated in patients with moderate or severe (Child-Pugh B or C) hepatic impairment • Some data suggest that ART-naive patients with high pre-NVP CD4 counts (>250 cells/mm^3 for females, >400 cells/mm^3 for males) are at higher risk of symptomatic hepatic events. NVP is not recommended in these patients unless benefit clearly outweighs risk. • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials
	RPV	• Once-daily dosing • Coformulated with TDF/FTC • Compared with EFV: - Fewer discontinuations for CNS adverse effects - Fewer lipid effects - Fewer rashes	• More virologic failures in patients with pretreatment HIV RNA >100,000 copies/mL than with EFV-based regimen • More NNRTI- and 3TC-associated mutations at virological failure than with regimen containing EFV + two NRTIs • Food requirement • Absorption depends on lower gastric pH. (See **Table 15a** for detailed information regarding interactions with H_2 antagonists and antacids.) • Contraindicated with PPIs • RPV-associated depression reported • Use RPV with caution when coadministered with a drug having a known risk of torsades de pointes.
PIs (in alphabetical order)		**PI Class Advantages:** • Higher genetic barrier to resistance than NNRTIs and RAL • PI resistance uncommon with failure (boosted PIs)	**PI Class Disadvantages:** • Metabolic complications such as dyslipidemia, insulin resistance, hepatotoxicity • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (more pronounced with RTV-based regimens) (See Tables 14 and 15a.)
	ATV	• Fewer adverse effects on lipids than other PIs • Once-daily dosing • Low pill burden (two pills per day) • Good GI tolerability • Signature mutation (I50L) not associated with broad PI cross resistance	• Indirect hyperbilirubinemia sometimes leading to jaundice or scleral icterus • PR interval prolongation: generally inconsequential unless ATV combined with another drug with similar effect • Cannot be coadministered with TDF, EFV, or NVP (See ATV/r.) • Nephrolithiasis • Skin rash • Food requirement • Absorption depends on food and low gastric pH. (See Table 15a for detailed information regarding interactions with H_2 antagonists, antacids, and PPIs.)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
	ATV/r	• RTV boosting: higher trough ATV concentration and greater antiviral effect • Once-daily dosing • Low pill burden (two pills per day)	• More adverse effects on lipids than unboosted ATV • More hyperbilirubinemia and jaundice than unboosted ATV • Food requirement • Absorption depends on food and low gastric pH. (See **Table 15a** for interactions with H_2 antagonists, antacids, and PPIs.) • RTV boosting required with TDF and EFV. With EFV, use ATV 400 mg and RTV 100 mg once daily (PI-naive patients only). • Should not be coadministered with NVP
	DRV/r	• Once-daily dosing • Potent virologic efficacy	• Skin rash • Food requirement
	FPV/r	• Twice-daily dosing resulted in efficacy comparable to LPV/r • RTV boosting: higher trough APV concentration and greater antiviral effect • Once-daily dosing possible with RTV 100 mg or 200 mg daily • No food effect	• Skin rash • Hyperlipidemia • Once-daily dosing results in lower APV concentrations than twice-daily dosing • For FPV 1,400 mg + RTV 200 mg: requires 200 mg of RTV and no coformulation • Fewer data on FPV 1,400 mg + RTV 100 mg dose than on DRV/r and ATV/r
	LPV/r	• Coformulated • No food requirement • Recommended PI in pregnant women (twice daily only) • Greater CD4 count increase than with EFV-based regimens	• Requires 200 mg per day of RTV • Lower drug exposure in pregnant women—may need dose increase in third trimester • Once-daily dosing not recommended in pregnant women • Once-daily dosing: lower trough concentration than twice-daily dosing • Possible higher risk of MI associated with cumulative use of LPV/r • PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or receiving other drugs with similar effect.
	SQV/r	• Efficacy similar to LPV/r with less hyperlipidemia	• Highest pill burden (6 pills per day) among available PI regimens • Requires 200 mg of RTV • Food requirement • PR and/or QT interval prolongations in a healthy volunteer study • Pretreatment ECG recommended • SQV/r is not recommended for patients with any of the following conditions: (1) congenital or acquired QT prolongation; (2) pretreatment ECG >450 msec; (3) on concomitant therapy with other drugs that prolong QT interval; (4) complete AV block without implanted pacemakers; (5) risk of complete AV block.
INSTI	**RAL**	• Virologic response noninferior to EFV • Fewer drug-related adverse events and lipid changes than EFV • No food effect • Fewer drug-drug interactions than PI- or NNRTI-based regimens	• Less long-term experience in ART-naive patients than with boosted PI- or NNRTI-based regimens • Twice-daily dosing • Lower genetic barrier to resistance than with boosted PI-based regimens • No data with NRTIs other than TDF/FTC in ART-naive patients
CCR5 Antagonist	**MVC**	• Virologic response noninferior to EFV in post hoc analysis of MERIT study (See text.) • Fewer adverse effects than EFV	• Requires viral tropism testing prior to initiation of therapy with additional cost and possible delay in initiation of therapy • More MVC-treated than EFV-treated patients discontinued therapy due to lack of efficacy in MERIT study • Less long-term experience in ART-naive patients than with boosted PI- or NNRTI-based regimens • Limited experience with two NRTIs other than ZDV/3TC • Twice-daily dosing • CYP 3A4 substrate, dosing depends on presence or absence of concomitant CYP3A4 inducer(s) or inhibitor(s)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
Dual NRTIs		**Dual-NRTI Class Advantage:** Established backbone of combination ART	**Dual-NRTI Class Disadvantage:** Rare but serious cases of lactic acidosis with hepatic steatosis reported with d4T, ddI, and ZDV
Dual-NRTI pairs (in alphabetical order)	**ABC/3TC**	• Virologic response noninferior to ZDV/3TC • Better CD4 count response than with ZDV/3TC • Once-daily dosing • Coformulation • No food effect • No cumulative TAM-mediated resistance	• Potential for ABC HSR in patients with HLA-B*5701 • Potential for increased cardiovascular events, especially in patients with cardiovascular risk factors • Inferior virologic responses in patients with baseline HIV RNA >100,000 copies/mL when compared with TDF/FTC in ACTG 5202 study; however, this was not seen in the HEAT study.
	TDF/FTC	• Better virologic responses than with ZDV/3TC • Better virologic responses than with ABC/3TC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study; however, this was not seen in the HEAT study. • Active against HBV; recommended dual-NRTI for HBV/HIV coinfection • Once-daily dosing • No food effect • Coformulated (TDF/FTC, EFV/TDF/FTC and RPV/TDF/FTC) • No cumulative TAM-mediated resistance	• Potential for renal impairment, including rare reports of Fanconi syndrome and acute renal insufficiency • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials • Potential for decrease in bone mineral density
	ZDV/3TC	• Coformulated (ZDV/3TC and ZDV/3TC/ABC) • No food effect (although better tolerated with food) • Preferred dual NRTI in pregnant women	• Bone marrow suppression, especially anemia and neutropenia • GI intolerance, headache • Mitochondrial toxicity, including lipoatrophy, lactic acidosis, hepatic steatosis • Inferior to TDF/FTC in combination with EFV • Less CD4 increase compared with ABC/3TC • Twice-daily dosing

Acronyms: 3TC = lamivudine, ABC = abacavir, APV = amprenavir, ART = antiretroviral therapy, ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir/ritonavir, AV = atrioventricular, CNS = central nervous system, CYP = cytochrome P, d4T = stavudine, ddI = didanosine, DRV/r = darunavir/ritonavir, ECG = electrocardiogram, EFV = efavirenz, FPV = fosamprenavir, FPV/r = fosamprenavir/ ritonavir, FTC = emtricitabine, GI = gastrointestinal, HBV = hepatitis B virus, HSR = hypersensitivity reaction, INSTI = integrase strand transfer inhibitor, LPV/r = lopinavir/ritonavir, MI = myocardial infarction, msec = milliseconds, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PPI = proton pump inhibitor, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, SQV/r = saquinavir/ritonavir, TAM = thymidine analogue mutation, TDF = tenofovir, ZDV = zidovudine

Table 7. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (Updated October 14, 2011)

ARV Drugs or Components (in alphabetical order)	Reasons for NOT recommending as initial therapy
ABC/3TC/ZDV (coformulated) as triple-NRTI combination regimen **(BI)**	• Inferior virologic efficacy
ABC + 3TC + ZDV + TDF as quadruple-NRTI combination **(BI)**	• Inferior virologic efficacy
ABC + ddI **(BIII)**	• Insufficient data in ART-naive patients
ABC + TDF **(BIII)**	• Insufficient data in ART-naive patients
DRV (unboosted)	• Use without RTV has not been studied
DLV **(BIII)**	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
ddI + 3TC (or FTC) **(BIII)**	• Inferior virologic efficacy, least clinical trial experience
ddI + TDF **(BII)**	• High rate of early virologic failure • Rapid selection of resistance mutations • Potential for immunologic nonresponse/CD4 T-cell decline • Increased ddI drug exposure and toxicities
T-20 **(BIII)**	• No clinical trial experience in ART-naive patients • Requires twice-daily subcutaneous injections
ETR **(BIII)**	• Insufficient data in ART-naive patients
FPV (unboosted) **(BIII)**	• Less potent than RTV-boosted FPV • Virologic failure with unboosted FPV-based regimen may select mutations that confer resistance to DRV
IDV (unboosted) **(BIII)**	• Inconvenient dosing (three times daily with meal restrictions) • Fluid requirement
IDV (RTV-boosted) **(BIII)**	• High incidence of nephrolithiasis
NFV **(BI)**	• Inferior virologic efficacy • High incidence of diarrhea
RTV as sole PI **(BIII)**	• High pill burden • GI intolerance
SQV (unboosted) **(BI)**	• Inferior virologic efficacy
d4T + 3TC **(BI)**	• Significant toxicities including lipoatrophy; peripheral neuropathy; and hyperlactatemia, including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis
TPV (RTV-boosted) **(BI)**	• Inferior virologic efficacy

Acronyms: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ARV = antiretroviral, d4T = stavudine, ddI = didanosine, DLV = delavirdine, DRV = darunavir, ETR = etravirine, FPV = fosamprenavir, FTC = emtricitabine, GI = gastrointestinal, IDV = indinavir,NFV = nelfinavir, NRTI = nucleoside reverse transcriptase inhibitor, RTV = ritonavir, SQV = sacquinavir, T-20 = enfuvirtide, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

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